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A New Target for Tumor Therapy

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Vascular normalization, or restoration of the normal structure and function in blood vessels, has emerged as a strategy to treat cancer and other vascular disorders.[1] Mazzone et al.[2] have recently proposed a new approach for vascular normalization — targeting the prolyl hydroxylase domain 2 (PHD2) protein, an oxygen sensor that tags hypoxia-induced transcription factors for degradation. These authors found that haplodeficiency (i.e., half the "normal" dose) of *PHD2* in endothelial cells "normalizes" abnormal endothelial cells in tumors, resulting in increased tumor oxygenation and decreased metastasis.[2]

In normal tissues, the balance between proangiogenic and antiangiogenic signaling maintains the normal structure of the endothelial-cell lining, surrounding pericytes, and vascular basement membrane in order to ensure optimal function. In tumors, because of genetic and epigenetic mechanisms (e.g., genetic mechanisms initiated by oncogenes and epigenetic mechanisms initiated by hypoxia), this balance is tipped toward the proangiogenic side, and hence the structure of the vessel wall becomes abnormal. The pericytes detach from endothelial cells, the basement membrane becomes too thin or too thick, and the endothelial lining becomes irregular and discontinuous. The net result is a dysfunctional vasculature that fuels tumor progression and resistance to therapy (Fig. 1).

Judicious application of direct or indirect anti-angiogenesis agents may thus restore the balance between proangiogenic and antiangiogenic signaling and thereby "normalize" the tumor vasculature (Fig. 1).[3] In addition to being more efficient for oxygen and drug delivery, the normalized vessels can prevent metastasis by hindering intravasation of cancer cells. Vascular normalization can also reduce tissue hypoxia and interstitial fluid pressure. Increased oxygen levels can sensitize cancer cells to radiotherapy and a number of chemotherapy drugs and increase the immune response to the tumor. Reduced interstitial fluid pressure can decrease tumor-associated swelling (edema) and reduce the likelihood of lymphatic metastasis. Independent of these effects, alleviation of hypoxia can decrease the selection pressure on cancer cells and thus prevent the evolution of a more malignant phenotype. These consequences of normalization have been validated in the research setting, and some of them have been validated in the clinical setting.[1]

The study by Mazzone et al. shows that, in mice, tumor endothelial cells that are haplodeficient in *PHD2* maintain the normal "cobblestone" morphologic features. This normalized endothelial-cell lining offers resistance to intravasation of cancer cells —

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resulting in decreased shedding of cancer cells into the circulation and ultimately less metastasis. The normalized vasculature also improves perfusion and reduces hypoxia in tumors (Fig. 1). Hypoxia is known to select for cancer cells that are invasive and motile. Thus, endothelial-cell normalization also reduces the invasion of cancer cells into blood and lymphatic vessels.

Mazzone et al. also offer a compelling molecular mechanism for endothelial-cell normalization by reduction in PHD2 activity. By stabilizing hypoxia-induced transcription factors, PHD2 haplodeficiency up-regulates both soluble and membrane-bound vascular endothelial growth factor (VEGF) receptor 1 (VEGFR-1) and VE-cadherin (an adhesion molecule) in endothelial cells. The soluble VEGFR-1 blocks the binding of excess VEGF — which is produced by cancer and other stromal cells in the tumor microenvironment — to VEGF receptors on the endothelial cells. This blockage, in turn, ensures that endothelial cells are quiescent. In concert, VE-cadherin tightens the endothelial-cell lining.

Mazzone and colleagues observed, however, that PHD2 haplodeficiency did not inhibit tumor growth in preclinical models. My laboratory has recently shown[4] that even in the face of persistent tumor growth, vascular normalization can prolong survival — in mice and possibly in patients with brain tumors — by alleviating tumor-associated edema. So, anti-PHD2 monotherapy might improve survival in some diseases. But to further prolong survival, anti-PHD2 therapy would have to be combined with agents that destroy cancer cells.

Anti-VEGF agents transiently normalize tumor vessels; the window of normalization lasts less than a week in preclinical models to a month in patients with recurrent glioblastomas.[1] Cytotoxic therapy given during this window leads to a better outcome than when the same therapy is given outside this window.[5] It would thus seem prudent to measure the duration of the normalization window created by anti-PHD2 agents. Another lesson learned through blocking the VEGF pathway is one of moderation; the pruning of too many tumor vessels compromises the delivery of cytotoxic therapies and causes hypoxia. Consistent with this lesson is the death of PHD2 knockout mice at midgestation. Therefore, the dose of PHD2-targeting agents will have to be carefully titrated. Finally, tumors develop resistance to anti-VEGF therapies by switching to other angiogenic pathways or methods of recruiting blood vessels for further growth.[1] As compared with malignant cells, endothelial cells are genetically stable, so there is less likelihood that they will develop resistance to anti-PHD2 agents, but this possibility cannot be discounted. These caveats notwithstanding, anti-PHD2 agents seem very likely to offer a new approach to treating cancer and other diseases characterized by abnormal blood vessels.

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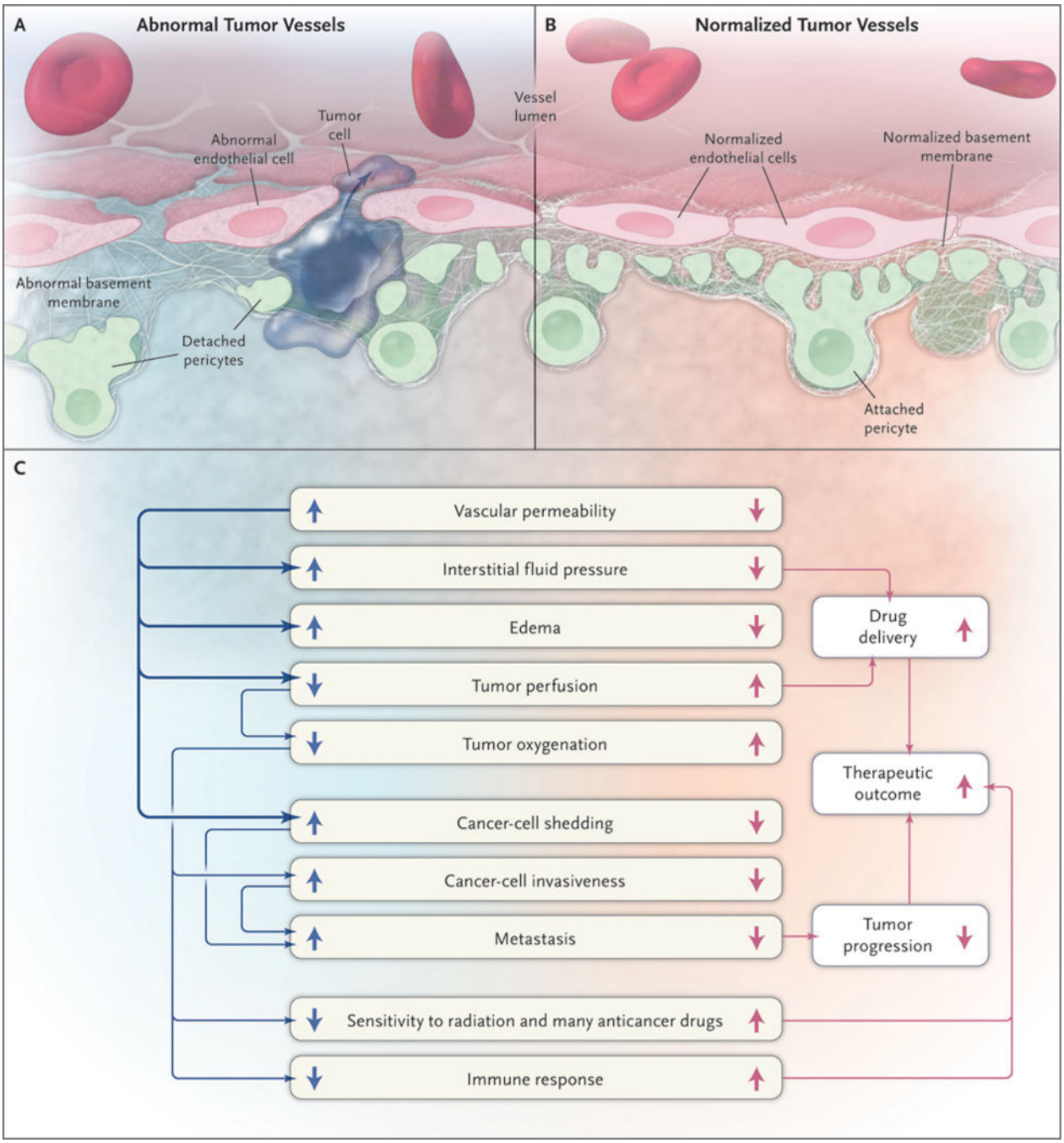

Figure 1. Normalizing Blood Vessels in Tumors

As shown in Panel A, tumor vessels have an abnormal endothelial-cell lining, detached pericytes, and a basement membrane that is abnormally thick or abnormally thin. These structural abnormalities — a result of excessive production of proangiogenic molecules such as vascular endothelial growth factor (VEGF) and downregulation of antiangiogenic molecules such as thrombospondin — can make tumor vessels hyperpermeable. As shown in Panel B, by restoring balance between proangiogenic and antiangiogenic signaling in the endothelial cells, the tumor vessels become normalized both structurally and functionally.

This normalization can decrease cancer-cell invasion into blood and lymphatic vessels, resulting in fewer shed cells in circulation and ultimately less metastasis. As shown in Panel C, leakiness reduces tumor perfusion and oxygenation. Reduced oxygen levels can impair the immune response, lower the efficacy of many anticancer therapies, and select for more invasive cancer cells. The blue arrows denote variables associated with abnormal vessels, and the red arrows denote variables associated with normalized vessels. A recent study by Mazzone et al.[2] shows that endothelial cells with reduced levels of the oxygen sensor PHD2 can normalize tumor vessels by up-regulating the production of soluble VEGF receptor 1 (VEGFR-1) and VE-cadherin (an adhesion molecule). The former mops up excess VEGF produced by a tumor before it binds to its signaling receptor VEGF receptor 2 (VEGFR-2) on endothelial cells, and the latter tightens junctions between endothelial cells, rendering a “tighter” lining of endothelial cells. These observations suggest that anti-PHD2 agents, once developed, could be used to reduce edema and sensitize tumor cells to radiation therapy and chemotherapeutic agents.